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Patient survival after renal transplantation: I. The impact of dialysis pre-transplant

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Patient survival after renal transplantation: I. The impact of dialysis pre-transplant. Patients on dialysis and recipients of renal transplants have higher mortality than individuals without kidney disease. In this study we evaluated the possible impact of dialysis therapy before transplantation on patient survival after the transplant. This analysis includes all of the patients who received a cadaveric renal transplant at The Ohio State University from 1984 to 1991 and who remained alive with functioning grafts for at least six months after the transplant ($N = 523$). After a follow-up of 84 ± 14 months, 28% of the patients died and 23% lost their grafts. By multivariate analysis, reduced patient survival (censored at the time of graft loss) correlated with these pre-transplant variables: Older age ($P < 0.0001$), the presence of diabetes ($P = 0.0002$), smoking ($P = 0.009$), and the length of time on dialysis ($P = 0.0002$). Thus, 7% of patients who were never dialyzed, 23% of those dialyzed for less than three years, and 44% of patients dialyzed for ≥ three years died post-transplant. By Cox regression, patient survival months correlated with time on dialysis pre-transplant ($P = 0.0003$). The type of dialysis (CAPD vs. hemodialysis) did not correlate with patient survival. Graft survival, censored for patient death, did not correlate with any of these pre-transplant variables. The relationship between time on dialysis and patient mortality is due to at least two factors: (*1*) transplant recipients who had dialysis for ≥ 3 years had higher mortality due to infections (22%) than those who had dialysis for < 3 years (3%, $P = 0.01$ by X^2); and (*2*) increasing time on dialysis increases the prevalence of both left ventricular hypertrophy ($P = 0.008$) and cardiomegaly ($P = 0.004$), and these relationships are statistically independent of other factors that also correlate with the prevalence of cardiovascular disease. In conclusion, increased time on dialysis prior to renal transplantation is associated with decreased survival of transplant recipients.

Despite dramatic advances in the field of renal transplantation, patient death continues to be a leading cause of renal transplant failure. In fact, in selected patient populations, such as in patients with diabetes [1, 2] and in smokers [3], patient death is the most common reason for renal transplant loss. The excess mortality of transplant recipients is mainly due to cardiovascular causes [4]. Several factors contribute to the excessive cardiovascular risk of renal transplant recipients, and these factors can be subdivided into two categories: (*1*) factors that are introduced at the time of transplantation, for example, worsening hypertension, hyperlipidemia and administration of corticosteroids; and (*2*) cardiovascular factors that are already present in the patient before the transplant. In fact, the evidence suggests that perhaps the majority of patients with renal disease acquire cardiovascular abnormalities prior to the initiation of dialysis, and that dialysis accelerates the development of cardiovascular disease. This evidence is as follows. Prior to the initiation of dialysis, patients frequently have evidence of cardiovascular disease, such as left ventricular hypertrophy (LVH), dilated cardiomyopathy, and history of congestive heart failure. The presence of some of these cardiovascular markers predict patient survival on dialysis [5–7]. Several studies have shown that prior to dialysis, the prevalence of LVH increases with increasing age, worsening renal function, anemia, and hypertension [8–10]. Sequential studies in patients maintained on hemodialysis indicate that the patient's cardiovascular risk profile may worsen with time on dialysis, particularly in patients with poorly controlled blood pressure (BP) [11, 12]. The modality of dialysis may also have implications for cardiovascular risk and/or patient survival. Several studies have shown that the mortality of patients on continuous peritoneal dialysis (CAPD) exceeds that of patients on hemodialysis (HD) [13, 14]. In apparent contrast with this observation, LVH is significantly more common in patients on HD than those on CAPD [15].

Based on the observations discussed above, in these studies we assessed whether patient survival post-transplant correlates with: (*1*) the length of time that the patient was treated with dialysis prior to the transplant, and/or (*2*) the type of dialysis that the patient received. The implications that these determinations may have for the care of the patient with end stage-renal disease are clear. However, initially one may conclude that there is little we can do to shorten the dialysis time pre-transplant, because most often the waiting period for renal transplantation is caused by the shortage of donor organs. However, it is our anecdotal experience that some patients are referred for renal transplantation only after they have been on dialysis for a certain period of time. Furthermore, there is sufficient evidence to conclude that improvements in the delivery of dialysis will reduce patient morbidity and mortality [16, 17], and the results of these studies suggest that

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improvements in dialysis delivery will also improve patient survival post-transplant.

METHODS

The population of patients studied here included all adult cadaveric kidney transplant recipients transplanted at The Ohio State University from August 1984 to November 1991. In addition, these patients met the following criteria. (*1*) Patients were alive with a functioning graft for at least six months following the transplant. (*2*) For patients alive with functioning allografts, the minimum period of follow-up was six years. (*3*) All patients were followed at our institution. The exclusion of patients who died shortly after transplantation was done in an effort to exclude surgical complications as a cause of death, because the main focus of this study was on long term patient mortality. Following transplantation, patients were treated with a uniform immunosuppressive protocol that has been previously described [18]. Briefly, immediately following the transplant, patients received induction immunosuppressive therapy with Minnesota anti-lymphocyte globulin or OKT3 (Ortho Biotech), azathioprine, and prednisone. Subsequently, once the patient's serum creatinine reached a concentration of 2.5 mg/dl or lower, the patient was started on cyclosporine (CsA) and maintained on combined therapy with prednisone and cyclosporine for the length of the follow-up. Those patients who required re-initiation of chronic dialysis therapy were considered as allograft failures.

Pre-transplant variables were collected by a review of outpatient and inpatient charts. Patients transplanted at our institution are referred from a rather wide geographic area covering principally Central and Southeast portions of the state of Ohio, portions of Kentucky and West Virginia. These patients received their pre-transplant medical care in several dialysis units and the care was provided by several nephrologists. Thus, the results of this analysis is likely to be representative of the effects of dialysis in our region and does not reflect the effects of dialysis care in a single center. The routine pre-transplant cardiovascular evaluation included an electrocardiogram (EKG) and a chest x-ray (CxR). A cardiac ultrasound was not done routinely as part of the pre-transplant evaluation. Consequently, the diagnoses of cardiomegaly in this study was based on radiologic criteria that is, the presence of a cardial silhouette that occupies more than 50% of the thoracic transverse diameter. The diagnosis of LVH was made by ECG, and were interpreted electronically by the Marquette Medical Systems (Marquette Electronics Inc, WI,), which is based principally on voltage criteria of LVH [19]. Furthermore, all ECG tracings were reviewed by cardiologists at Ohio State University who customarily made the diagnosis of LVH based on published criteria [20]. Pre-transplant blood pressure (BP) levels were collected at several time points including prior to dialysis, during hospitalization prior to the transplant, and during the patient's pre-transplant work-up. All of these BP levels were averaged and the mean arterial pressure (MAP) was calculated by the following formula: [(systolic BP-diastolic BP)/3) + diastolic BP]. Post-transplant parameters were retrieved from a computerized database that included all post-transplant laboratory tests, BP recordings, and hospitalizations. Blood pressure levels were measured by the patient at home and the results called to our transplant center. The diagnosis of acute rejection, in our institution, is always based on both clinical (that is, acute elevation of serum creatinine) and pathologic criteria [21].

Table 1. Patient characteristics prior to transplantation

Parameters	Value
Number of patients	523
Age *years*	43 ± 13
Gender *% males*	59%
Race *% Caucasians*	78%
Weight *kg*	70.7 ± 18
Diabetes	25%
Smoking *%*	42%
Cardiomegaly	33%
LVH by EKG	28%
Dialysis time *months*	17.6 ± 18
Dialysis type	
No dialysis	29 (6%)
Hemodialysis (HD)	319 (66%)
CAPD	96 (20%)
HD/CAPD	38[a] (8%)
Mean MAP pre-transplant	108 ± 14
Hypertensive[b] (% patients)	227 (43%)

[a] Thirty-six patients had HD first and then CAPD; 2 patients had CAPD first and then HD

[b] Percent of patients with MAP ≥ 107 mm Hg (~140/90). The majority of these patients were taking antihypertensive medications (4,257) at the time of determination of BP.

The cause of the patient's demise was obtained from diagnoses included in the patient's death certificate, and these data were obtained from files maintained in the United States Renal Data System (USRDS) [14]. Information on the primary cause of death was available in 101 of the 144 patients who died (70%). However, information on secondary causes of death was available in only very few patients, and for this reason these latter data were not analyzed.

Statistical analysis

Values are expressed as means ± SD throughout the manuscript. The means of normally distributed data were compared by Student's *t*-test, and when the data were not normally distributed, by non-parametric test (Mann-Whitney). Chi square was used to compare percentages. Linear regression and non-parametric correlations (Spearman) were used to analyze relationships among data. Cox proportional hazards and Kaplan-Meier plots were used to estimate patient and graft survival. Patient survival was censored at the time of allograft loss. Graft survival was analyzed with and without censoring for patient death as it will be indicated.

RESULTS

Patient characteristics pre-transplant

Table 1 displays the patient characteristics. By study design, all patients were alive and had functioning renal grafts for at least six months post-transplant. The average period of follow-up for the population was 84 ± 41 months. During this period, 28% of the patients died and 23% lost their graft for causes other than patient death.

Relationships between pre-transplant variables and patient survival

Table 2 displays results of univariate and multivariate correlations between pre-transplant variables and patient survival. As can be seen, reduced patient survival correlated with increasing age,

Table 2. Correlation between pre-transplant variables and patient survival after renal transplantation

Parameter	Univariate analysis	Multivariate analysis
Age	<0.0001	<0.0001
Race	NS	—
Gender	NS	—
Weight	NS	—
Diabetes	0.0002	0.0002
Blood pressure[a]	NS	—
LVH by EKG	NS	—
Cardiomegaly	0.0005	NS[b]
Smoking	0.004	0.009
Type of dialysis	NS	—
Time on dialysis	0.0005	0.0002

Analyses were done by univariate and multivariate logistic regression analysis.

[a] Blood pressure was analyzed as systolic BP or MAP with similar results

[b] The variable cardiomegaly was not significantly correlated with survival if "time on dialysis" was included in the multivariate model

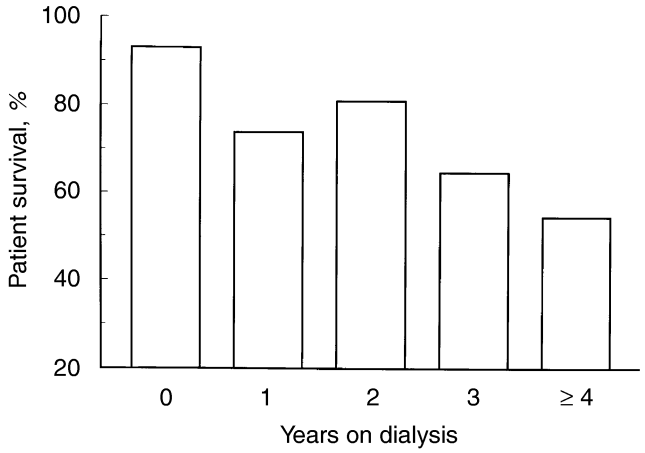

Fig. 1. Relationship between time on dialysis (x axis) and patient survival after renal transplantation. The number of patients in each group is according to their duration on dialysis: 0 year, $N = 29$; 1 year, $N = 205$; 2 years, $N = 137$; 3 years, $N = 45$; ≥ 4 years, $N = 46$.

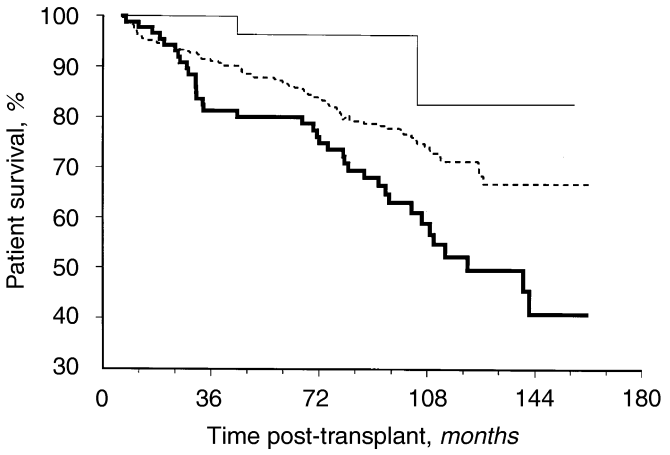

Fig. 2. Kaplan-Meier plots of patient survival. Patients were divided into three groups according to the time that they had spent on dialysis (any modality) prior to transplantation: No dialysis (–); 1 to 2 years (¼); or ≥ three years (▬). Cox regression: $P = 0.0003$.

diagnosis of diabetes, smoking, the presence of cardiomegaly, and increasing periods of time on dialysis. By multivariate analysis, older age, the presence of diabetes, a history of smoking, and the length of time on dialysis correlated significantly with patient mortality (Table 2). In contrast, cardiomegaly did not correlate with patient mortality as long as the parameter "time on dialysis" was also incorporated in the multivariate model. However, if this latter parameter was excluded from the model, cardiomegaly correlated with patient mortality independently from age, smoking, or diabetes. Blood pressure levels, analyzed as systolic BP or as MAP did not correlate with patient mortality post-transplant (Table 2).

The relationship between time on dialysis and patient survival is displayed graphically in Figure 1. To further analyze the effect of time on dialysis on patient survival, patients were divided into three groups: (*1*) 29 patients never received dialysis prior to the transplant; (*2*) 342 patients were on hemodialysis or CAPD for one to two years; and (*3*) 91 patients had received dialysis (any modality) for at least three years. In the remaining patients we could not precisely determine the time they had spent on dialysis. Patient mortality among these three groups of patients were 7%, 23% and 41%, respectively ($P < 0.0001$, X^2). It should be noted that patients who had been maintained on dialysis for relatively short periods of time (1 to 2 years) had a significantly higher mortality than patients who never received dialysis, although that latter group of patients is small (mortality in group 1 vs. group 2, $P < 0.04$ by X^2). By the Cox regression, the length of patient survival after the transplant was also significantly different among these three groups of patients ($P = 0.0003$). Figure 2 displays Kaplan-Meier plots of patient survival in these three groups of recipients.

The modality of dialysis had no statistically significant effect on patient mortality (Table 2). Thus, 17% of the patients who received CAPD and 23% of the patients who received HD died after transplantation (NS). In contrast, 43% of the 38 patients who received both HD and CAPD prior to the transplant died, and the mortality rate of these individuals is significantly higher than the mortality rate of patients who received HD alone (23%, $P = 0.01$ by X^2) or CAPD alone (17%, $P = 0.003$ by X^2). The higher mortality of patients who received both HD and CAPD could not be explained by differences in age, smoking, length of time on dialysis, or the prevalence of LVH or cardiomegaly.

Patient survival did not correlate significantly with the following post-transplant parameters (collected during the first six months following the transplant): allograft function, number of rejection episodes, average BP levels, lipid levels (total cholesterol or triglycerides), or cumulative doses of prednisone or cyclosporine.

Because patient survival was censored at the time of graft loss, it is important to note that none of the parameters listed in Table 2, and in particular time on dialysis, correlated statistically with death-censored graft survival (data not shown). However, pre-transplant variables had important consequences for the overall success of renal transplantation. For example, increasing time on dialysis correlated with shorter renal allograft survival, when the graft survival data were not death censored (Fig. 3A; Cox

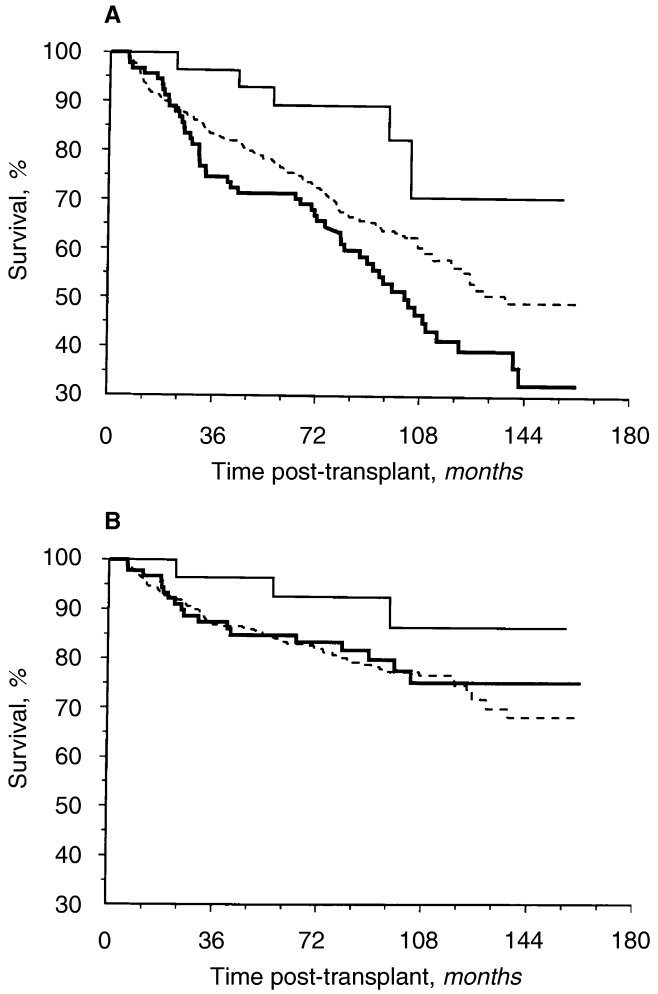

Fig. 3. (*A*) Graft survival in kidney transplant recipients divided according to the time that the patient was on dialysis prior to the transplant: no dialysis (–); 1 to 2 years of dialysis (¼); 3 years on dialysis (━) by Cox regression, $P = 0.003$; (*B*) death censored kidney graft survival (Cox regression, NS). Patients were divided into the same groups described in A.

Table 3. Patient's characteristics according to the period of time that they spend on dialysis prior to transplantation

Parameter	Time on dialysis (years) 0	1–2	≥3	Statistics[a]
Number of patients	29	342	91	
Age	42 ± 13	43 ± 12	44 ± 14	NS
Gender *% Males*	48%	37%	44%	NS
Race *% Blacks*	21%	20%	32%	.05
Weight *kg*	73 ± 16	72 ± 16	70 ± 20	NS
Diabetes	21%	27%	21%	NS
Smoking	46%	43%	35%	NS
Blood pressure	109 ± 10	108 ± 14	108 ± 13	NS
LVH by EKG	14%	26%	39%	0.01[b]
Cardiomegaly	15%	31%	45%	0.007[c]
Type of dialysis *% HD*	—	68%	78%	NS

[a] Proportions were compared by Chi square and means were compared by ANOVA
[b] $P = 0.003$ by logistic regression analysis
[c] $P = 0.0006$ by logistic regression analysis

Table 4. Pre-transplant variables that correlate with the prevalence of cardiomegaly or LVH prior to transplantation

Parameter	Cardiomegaly Univariate	Cardiomegaly Multivariate	LVH Univariate	LVH Multivariate
Age	0.004	NS	0.03	NS
Race	<0.0001	0.001	<0.0001	0.001
Gender	NS	—	0.004	0.006
Weight	NS	—	NS	—
Diabetes	NS	—	NS	—
Blood pressure (systolic)	0.005	0.01	0.0002	0.001
Smoking	NS	—	NS	—
Type of dialysis	NS	—	0.03	0.04
Time on dialysis	0.0006	0.004	0.003	0.008

Univariate and multivariate logistic regression analyses were used.

regression, $P = 0.003$). In this analysis, graft survival was significantly better in patients who never received dialysis than in those who had dialysis for one to two years (Cox regression, $P = 0.04$), and graft survival was also significantly better in patients who received dialysis for one to two years than in those who received dialysis for longer periods of time (Cox regression, $P = 0.03$). In contrast to these results, the time on dialysis did not correlate significantly with death-censored graft survival (Fig. 3B; Cox regression, $P = 0.6$).

Relationship between time on dialysis and cardiovascular factors

To try to determine the reason for the association between time on dialysis and patient mortality, we evaluated the pre-transplant characteristics of patients divided according to the time they had spent on dialysis (Table 3). As can be seen, the prevalence of LVH increased with increasing time on dialysis (any modality) ($P = 0.01$ by X^2 and $P = 0.003$ by logistic regression). Similarly, the prevalence of cardiomegaly also increased with time on dialysis ($P = 0.007$ by X^2 and $P = 0.0006$ by logistic regression).

Because other factors contribute to the development of cardiovascular factors, we next assessed whether the relationship between time on dialysis and cardiovascular parameters is related to some of these other covariates. Table 4 displays univariate and multivariate analysis of the relationships between pre-transplant variables and cardiomegaly or LVH. As can be seen the prevalence of these cardiovascular abnormalities increases with increasing age, Black race, elevated BP levels, and increasing time on dialysis. Furthermore, the prevalence of LVH was significantly higher in males (33%) than in females (21%, $P = 0.004$, by X^2); and in patients treated with HD (33%) compared to those treated with CAPD (23%, $P = 0.04$ by X^2). By multivariate analysis (Table 4), the relationship between time on dialysis and cardiomegaly is statistically independent from other factors associated with this cardiovascular marker. Similarly, the relationship between time on dialysis and LVH is statistically independent from other correlates of LVH.

Causes of death

Analysis of the primary cause of death reported in the patient's death certificate (Table 5) showed that death due to infection was significantly more common in patients maintained on dialysis for

Table 5. Causes of death post-transplant in patients who had been maintained on dialysis prior to transplantation

	Dialysis 1–2 years	Dialysis ≥3 years	Chi square
Number of patients	57	24	
Cause of death			
Cardiovascular[B]	30 (53%)	9 (38%)	NS
Cerebrovascular	4 (13%)	3 (13%)	NS
Infections	3 (4%)	5 (21%)	0.01
Malignancy	3 (5%)	1 (4%)	NS
Other	8 (14%)	3 (13%)	NS
Unknown cause	10 (18%)	3 (13%)	NS

[B] Includes in descending order of prevalence: acute myocardial infarction, cardiopulmonary arrest, arrhythmia, other cardiovascular causes, and atherosclerotic heart disease.

three or more years (21%) compared to those maintained on dialysis for less than three years (4%). The prevalence of all other causes of death was not statistically different between both groups of patients. Analysis of specific cardiovascular causes of death, for example, acute myocardial infarction or cardiopulmonary arrest, did not disclose significant differences between patients dialyzed for less or more than two years (data not shown). The group of patients that did not receive dialysis included only two patients who died, and thus, it was not possible to compare the causes of death in patients who received dialysis prior to the transplant and those who did not.

DISCUSSION

The findings of this study emphasize the need to consider the mortality of patients with end-stage renal disease (ESRD) as the result of the accumulation of risk factors starting at the time of initiation of renal disease, worsening as the renal function decreases [5], and progressing when dialysis is initiated [11]. Previous studies have shown that the mortality of patients who received renal transplants is significantly lower than the mortality of patients on dialysis (such as [14]), suggesting that transplantation may reverse, at least partially, the factors that cause the high mortality of dialysis patients. Consistent with this postulate, studies by Parfrey et al [22] indicate that left ventricular mass decreases following renal transplantation. However, this beneficial effect of renal transplantation is partially negated by the introduction of new risk factors, such as worsening of blood pressure control [23], immunosuppressants, etc. Despite the beneficial and detrimental effects of transplantation, the results of this study indicate that pre-transplant variables still predict patient survival after renal transplantation.

These results confirm the findings of several previous studies showing that among transplant recipients, older patients [24] and those with diabetes [25] have a higher mortality than younger and nondiabetic patients, respectively. In addition, these studies emphasize the impact of at least two additional pre-transplant factors on patient mortality: (*1*) increasing time on dialysis; and (*2*) smoking. The impact of smoking on patient survival post-transplant will be addressed in a separate manuscript [3]. The consequences of dialysis are such that even relatively short periods of time on dialysis (1 to 2 years) are associated with a significant increase in patient mortality and an increase in failure of renal transplantation due to patient's demise. It can be argued that these findings may be due to patient selection, because perhaps younger and healthier patients with ESRD may be transplanted sooner than other patients. However, this argument is not supported by these data. For example, there were not significant age differences between patients who received dialysis and those who did not. In addition, although patients who received dialysis have a higher prevalence of LVH and cardiomegaly, these data and other studies suggest that this association is due to worsening of cardiovascular disease with time on dialysis (Table 4 and [11]) and not due to patient selection.

These results suggest that cardiomegaly (by CxR) is a better predictor of patient survival than LVH (by EKG). However, the interpretation of these data are limited by the fact that in these studies the precise anatomy of the left ventricle was not defined by cardiac ultrasound. Indeed, previous studies have shown that the geometry of the LV correlates with patient survival on dialysis [6]. Because cardiomegaly correlates with patient survival, and because increasing time on dialysis is associated with a higher prevalence of cardiomegaly, it is likely that cardiovascular factors explain, at least in part, the relationship between time on dialysis and patient survival. This postulate was not confirmed by examination of the cause of death specified in death certificates. However, this analysis is limited for at least two reasons: (*1*) We were unable to obtain information about the cause of death in 30% of the patients; and (*2*) We suspect that cardiovascular diagnoses included in death certificates are frequently presumed rather than proven. Based on these two reasons, we would not dismiss the postulate that time on dialysis pre-transplant increases the cardiovascular risk of renal transplant recipients, and thus their mortality.

This study also showed that patients maintained on dialysis for more than three years demonstrate higher mortality due to infectious causes than patients on dialysis for a shorter period of time. We give credence to this observation because it is likely that the inclusion by a physician of the diagnosis of "death due to infection and/or sepsis" in a death certificate is most likely based on objective evidence of active infection at the time of patient's death. Furthermore, there is abundant evidence in the literature that renal failure and/or dialysis has immunosuppressive effects [26, 27], and in fact, infection is only second to cardiac arrest as the single most common cause of death in patients with ESRD, particularly those on dialysis [14]. It is also quite possible that the higher rate of infections in patients maintained on dialysis for prolonged period of time may be related to malnutrition that is a frequent complication of prolonged dialysis therapy. Malnutrition can be assessed by measuring serum albumin levels [28, 29]. Unfortunately, results of albumin levels pre-transplant were not available for analysis in this study. Consistent with these results, previous studies showed that in recipients of kidney-pancreas allografts, graft loss due to infection was significantly higher in patients who received dialysis pre-transplant compared to those patients who did not receive dialysis [30].

The type of dialysis that the patient received prior to transplantation did not correlate with survival. However, it is of interest that patients who were switched from HD to CAPD had a higher mortality than any of the other groups of patients included in this study. The reasons for the high mortality of this patient group is unclear, but this analysis did not disclose significant differences between these patients and others in the prevalence of variables that correlate with patient survival. We postulate that the high mortality of patients who received both HD and CAPD indicates

that other pre-transplant factors not considered here, also correlate with patient survival [31].

Since 1991 (the most recent transplant year in the population of patients included in this study) important changes have been introduced in the practice of dialysis, and it is reasonable to expect that those changes will cause a reduction in patient morbidity and mortality [14, 17]. However, it is of concern that this recent emphasis in improving dialysis treatment by increasing solute clearance has not been associated with an equal emphasis in improving blood pressure and volume control, parameters that clearly correlate with the development of cardiovascular disease in ESRD patients [11]. It is likely that differences in the quality of the dialysis treatment and in the control of other cardiovascular risk factors explain the rather stricking differences in patient mortality among dialysis centers [16]. This study predicts that improvements in the quality of dialysis treatment are likely to improve not only patient survival during dialysis but also after transplantation.

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